MEETING SUMMARY
NATIONAL TOXICOLOGY PROGRAM
CENTER FOR THE EVALUATION OF RISKS
TO HUMAN REPRODUCTION
EXPERT PANEL EVALUATION of HYDROXYUREA
JANUARY 24–26, 2007

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) convened an expert panel on January 24–26, 2007, in Alexandria, Virginia to evaluate hydroxyurea. Hydroxyurea is used in the treatment of cancer, sickle cell disease, and thalassemia. It is the only treatment for sickle cell disease used in children aside from blood transfusion. Hydroxyurea may be used in the treatment of children and adults with sickle cell disease for an extended period of time or for repeated cycles of therapy. Treatment with hydroxyurea may be associated with cytotoxic and myelosuppressive effects and hydroxyurea is mutagenic. Hydroxyurea is FDA-approved for reducing the frequency of painful crises and the need for blood transfusions in adults with sickle cell anemia who experience recurrent moderate to severe painful crises. CERHR selected hydroxyurea for expert panel evaluation because of (1) increasing use in the treatment of sickle cell disease in children and adults, (2) knowledge that it inhibits DNA synthesis and is cytotoxic, and (3) published evidence of reproductive and developmental toxicity in rodents.

The expert panel, composed of 13 independent scientists, reviewed and evaluated the available scientific evidence on hydroxyurea in three primary areas: human exposure, reproductive toxicity, and developmental toxicity. They considered the quality, quantity, and strength of the evidence in their deliberations about the potential for hydroxyurea to cause adverse effects on human reproduction and/or prenatal or postnatal development. The expert panel also identified data gaps and research needs. All panel members serve as individual experts and not as representatives of their employers or other organizations.

Expert Panel Conclusions on Hydroxyurea

1. **The Expert Panel has concern that hydroxyurea may increase the risk of congenital anomalies or abnormalities of fetal growth and postnatal development after exposure of pregnant women.** This conclusion is based on the animal data indicating that hydroxyurea produces congenital anomalies and abnormalities of fetal growth in multiple experimental species. Data in experimental animals show that exposure levels causing developmental toxicity produce blood concentrations similar to those achieved in patients on therapy. The Expert Panel recognizes that hydroxyurea is used to treat serious illnesses and that the decision to use hydroxyurea by a woman of reproductive age or by a pregnant woman is made by the patient and her clinician.[1]
2. **The Expert Panel has minimal concern about the adverse effect of hydroxyurea on growth in children exposed to therapeutic doses of**

[1] The Expert Panel recognizes that some states require involvement of parents in reproductive health-related decisions affecting minor children.

hydroxyurea at 5–15 years of age. The growth studies were limited by lack of long-term follow-up. There are inadequate data on growth effects in infants and children younger than 5 years.

3. **The Expert Panel has concern about the adverse effect of hydroxyurea on spermatogenesis in men receiving hydroxyurea at therapeutic doses.** This conclusion is based on experimental animal data in rats and mice showing decreased testis weight and sperm count. Dose levels that caused adverse effects in the experimental animal studies are expected to produce blood concentrations that are similar to those achieved in patients on therapy. There are no data on the fertility of experimental animals after treatment with hydroxyurea. The Expert Panel recognizes that hydroxyurea is used to treat serious illnesses and that the decision to use hydroxyurea by a man of reproductive age is made by the patient and his clinician.[2]

The conclusions noted above are those of the Hydroxyurea Expert Panel and should not be construed to represent the views of the NTP.

Next Steps

The final expert panel report on hydroxyurea will be posted on the CERHR web site (http://cerhr.niehs.nih.gov) and available in printed text from the CERHR in April, 2007. The CERHR will solicit public comments on the report through an announcement in the Federal Register. Following this comment period, the CERHR will prepare the NTP-CERHR monograph on hydroxyurea, consisting of an NTP brief, expert panel report, and all public comments on that report. The monograph will be available to the public and on the CERHR web site and in hardcopy and will be sent to appropriate federal health and regulatory agencies.

Background

The NTP established the CERHR in 1998 as a public resource for providing scientifically based, uniform assessments of the potential for adverse effects on reproduction and/or development caused by man-made or naturally occurring chemicals or chemical mixtures to which humans are exposed. The CERHR convenes independent panels of scientific experts to conduct its evaluations. Expert panel meetings are open to the public and the public is invited to nominate scientists to serve on CERHR expert panels. Following completion of the evaluation of a chemical, the NTP prepares an NTP-CERHR monograph that contains its opinion on the potential for the chemical to be a reproductive or developmental hazard, the expert panel report, and public comments received on the final expert panel report. NTP-CERHR monographs on other chemicals evaluated by CERHR include seven phthalates, methanol, 1-bromopropane, 2-bromopropane, ethylene glycol, propylene glycol, fluoxetine (Prozac®), acrylamide, amphetamines, methylphenidate, and styrene and are available on the CERHR web site.

Questions about the expert panel review or CERHR can be directed to Dr. Michael Shelby, CERHR Director at 919-541-3455 or shelby@niehs.nih.gov .

[2]The Expert Panel recognizes that some states require involvement of parents in reproductive health-related decisions affecting minor children.